General

Guideline Title

Muscle invasive and locally advanced/metastatic bladder cancer.

Bibliographic Source(s)

Alberta Provincial Genitourinary Tumour Team. Muscle invasive and locally advanced/metastatic bladder cancer. Edmonton (Alberta): CancerControl Alberta; 2013 Oct. 17 p. (Clinical practice guideline; no. GU-002). [85 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Genitourinary Tumour Team. Bladder cancer. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Jan. 16 p. (Clinical practice guideline; no. GU-002).

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 14, 2016 – General anesthetic and sedation drugs : The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children's brain development.

Recommendations

Major Recommendations

Management of Stage T2a/b

Staging

- Computed tomography (CT) abdomen and pelvis or magnetic resonance imaging (MRI) as clinically indicated
- Examination under anesthesia and/or cystoscopy, if clinically indicated
- Chest x-ray (CXR)
- Alkaline phosphatase
- Bone scan, if elevated alkaline phosphatase or symptoms

Preparation for Therapy

- Baseline complete blood count (CBC)
- Baseline creatinine (Cr)

Therapy with Curative Intent

- Complete resection or adequate tissue sampling including muscularis propria.
- Either a surgical (radical cystectomy with full bilateral pelvic lymph node [LN] dissection) or a bladder preservation approach can be considered.
- Patients should be considered on an individual basis:
    - Bladder preservation is not preferred in patients with hydronephrosis or in patients with significant irritative symptoms.
    - Bladder preservation therapy is best suited for those with a solitary early-stage lesion, no carcinoma in situ (CIS), no evidence of hydronephrosis, adequate renal function for delivery of concurrent platinum-based chemotherapy, adequate bladder volume and absence of significant lower urinary tract symptoms.
    - Non-transitional cell histologies (i.e., adenocarcinoma, squamous-cell carcinoma) are generally insensitive to chemotherapy; these patients should not be considered for a neoadjuvant treatment.
    - In patients unable to tolerate either a surgical or bladder-preserving approach due to medical comorbidities, poor performance status, or unwillingness, consider transurethral resection of bladder tumour (TURBT) ± radiotherapy or chemotherapy, TURBT alone, radiotherapy alone, or chemotherapy alone.

Surgical Approach

- Ileal neobladder reconstruction can be considered in carefully selected patients with bladder-confined, node-negative urothelial carcinoma with good kidney and liver function.
- Radical cystectomy with bilateral pelvic lymph node dissection (PLND), followed by urinary diversion. Options for urinary diversion include continent reservoir and conduit diversion. There is insufficient data to recommend one procedure over another.
- Extended template PLND to include the presacral and common iliac lymph nodes to the aortic bifurcation.
- All patients who are eligible for cisplatinum-based combination chemotherapy should have the opportunity to discuss neoadjuvant therapy with a medical oncologist either before surgery or as combined modality therapy.
- Consider adjuvant chemotherapy based on pathological criteria (pT3-4, positive nodes), if no neoadjuvant chemotherapy is given.

Bladder-Preserving Approach

- Bladder preservation consists of radiotherapy combined with platinum-based chemotherapy.
- Prior to bladder preservation there should be a complete resection of the bladder tumour; if more than 8 weeks have elapsed since TURBT, or symptoms are recurrent, consider repeat TURBT prior to initiation of concurrent chemoradiation if safely possible.
- Consider surgical intervention (i.e., decompression) if hydronephrosis is present.
- Radiotherapy should be delivered to the whole bladder and regional nodes to at least 40 Gy, followed by a bladder/tumour boost to at least 60 Gy in conventional fractionation; altered fractionation regimens, such as 50–52.5 Gy in 20 fractions, may also be considered.
- In cystectomy candidates, second-look cystoscopy ± biopsy and urine cytology is recommended after 40–50 Gy to ensure complete response.
- Salvage cystectomy should be performed in patients with residual disease.

Neoadjuvant/Adjuvant Chemotherapy Peri-cystectomy

- Chemotherapy is usually given as cisplatinum-based combination therapy (e.g., cisplatinum, 70 mg/m^2 day 1 and gemcitabine, 1,000–1,250 mg/m^2 day 1 and 8 q 21 days); patients with contraindications to cisplatinum should proceed directly to definitive therapy—routine use of carboplatinum-based neoadjuvant combinations cannot be advised.
- Following neoadjuvant chemotherapy patients should have a CT scan of abdomen and pelvis, prior to the cystectomy.
- The standard of care for patients who have already undergone cystectomy is to offer adjuvant chemotherapy (same as neoadjuvant

chemotherapy regimen) T2 and T3 lesions or worse; if patients are ineligible for cisplatinum-based combination therapy in the adjuvant setting, carboplatinum-based combination therapy can be considered.

Chemotherapy Dose and Schedule for Combined Modality Approach

- For combined modality therapy, regimens include:
  - Cisplatinum 50 mg/m^2 is administered every 2 weeks during radiotherapy (RT); alternatively, usually for impaired renal function, carboplatinum (area under the curve [AUC] 1.5) weekly can be administered.
  - Cisplatinum 20 mg/m^2 days 1–4 q 21 days while receiving radiotherapy or, for patients in whom cisplatinum is contraindicated, carboplatinum administered at AUC 5 q 21 days can be considered.
  - 5-fluorouracil (5-FU; 500 mg/m^2 per day) during fractions 1–5 and 16–20 of RT and mitomycin C (12 mg/m^2) on day 1 can be considered.
- In patients who are candidates for a cystectomy a second look cystoscopy is recommended after 40–45 Gy to ensure appropriate therapeutic response.

Follow-up

Surgical Approach

- Urine cytology q 3 to 6 months for 3 years, then at increasing intervals
- CT abdomen and pelvis at 6 months as clinically indicated
- CXR q 6 months for 3 years, then at increasing intervals
- Duration: as clinically indicated; if there is no evidence of recurrence, could probably stop at 5 years

Bladder Preservation Approach

- Cystoscopy ± biopsy and cytology q 3 months for 1 year, then at increasing intervals
- CT abdomen and pelvis q 3 to 6 months for 2 years, then at increasing intervals
- CXR q 6 months for 3 years, then at increasing intervals
- Duration: as clinically indicated; if there is no evidence of recurrence, could probably stop at 5 years

Management of Stages T3, T4 and/or N1-3 M0

Indications include lymph node metastases *or locally advanced cancer* found at time of cystectomy.

Staging

- CT abdomen/pelvis
- CBC, biochemical profile
- CXR

Primary Therapy

- Radical cystectomy; if at the time of radical cystectomy the patient is found to have locally advanced disease or lymph node metastases, adjuvant chemotherapy can be considered.
- If cystectomy is abandoned because of locally extensive disease, concurrent chemoradiation can be considered as in the organ preservation approach, combined with 4 cycles of adjuvant chemotherapy; the patient should be made aware that the use of adjuvant chemotherapy is controversial in this setting.
- If surgery is abandoned because of unresectable N+ or T4b, the patient should be managed as for metastatic disease.
- Patients with muscle invasive disease who have not had surgical intervention may still be candidates for a combined modality approach.
  - These patients should also be considered for neoadjuvant chemotherapy prior to definitive local management.
  - The chemotherapy choice would be the same as described in the section, *Chemotherapy Dose and Schedule for Combined Modality Approach*, and should consist of a cisplatin-based regimen.
- Some patients may also be treated with single modality therapy, i.e., chemotherapy or radiotherapy for palliation and or survival prolongation.

Follow-up

Surgical Approach

- Cystectomy: clinical evaluation every 6, 12, and 24 months with a CXR, for 3 years.
- CT scan of abdomen and pelvis at 6 months post completion of therapy.
- Duration: as clinically indicated; if there is no evidence of recurrence, could stop at 5 years.

Bladder Preservation Approach

- Cystoscopic evaluation every 3 months for the first year with a CXR every 6 months for 3 years and then at increasing intervals.
- CT scan of the abdomen and pelvis should be done at 6 months post completion of therapy.
- Duration: as clinically indicated; if there is no evidence of recurrence, could stop at 5 years.

Management of Advanced Unresectable Metastatic Disease (T4b, N1-3, M1)

Indications include the development of metastatic disease post radical therapy or presents with advanced unresectable or metastatic disease.

Staging

- As clinically indicated:
  - CT abdomen/pelvis
  - CBC, renal and liver function tests
  - Bone scan if clinically indicated

Primary Therapy

- In patients who present with de novo metastatic disease or for those that develop metastatic disease after a definitive local therapy, the mainstay of treatment is systemic chemotherapy.
  - Cisplatinum in combination with gemcitabine is the primary chemotherapy combination at the dose and schedule described above; an alternative if clinically indicated is carboplatinum in combination with gemcitabine; patients who respond should be treated for a maximum of 6 cycles.
- For patients with their bladder *in situ*, radiotherapy to the bladder either as a single modality therapy or combined with a platinum can be administered for (1) palliation in patient unable to receive chemotherapy or (2) in attempt to reduce the risk of local recurrence as an adjunct to systemic chemotherapy in selected patients who wishes for aggressive treatment after discussion of lack of high level evidence in this area.
- Radiotherapy is of value in the management of symptomatic local disease and metastases.

Second-line

- There is no phase III data to support recommending one agent over another.
- If patients treated with cisplatinum (carboplatinum) + gemcitabine relapse within 6 months, consider treating with agents not previously administered such as cisplatin, methotrexate, vinblastine (CMV) or methotrexate, vinblastine, adriamycin, and cisplatinum (MVAC), depending on performance status, or single agents. If relapses are greater than six months, then the patient could be considered for re-treatment with original regimen or alternatively with CMV or MVAC.
- Paclitaxel in combination with a platinum agent could be considered as second-line therapy.

Follow-up

- Post-chemotherapy: CT scan to evaluate tumour response and then as clinically indicated to follow the course of the disease.
- If relapses are to occur, they are likely to happen early; therefore, follow closely for 2 years, and then as clinically indicated.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Muscle invasive and locally advanced/metastatic bladder cancer

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Internal Medicine

Oncology

Radiation Oncology

Radiology

Surgery

Urology

Intended Users

Physicians

Guideline Objective(s)

To provide physicians with the latest evidence-based management strategies for bladder cancer in Alberta

Target Population

Patients with muscle invasive bladder cancer (i.e., stages T2a/b, T3a/b, T4a and N0-X, M0)

Interventions and Practices Considered

Evaluation/Staging

1. Computed tomography (CT), abdomen/pelvis (with contrast) or magnetic resonance imaging (MRI)
2. Examination under anesthesia and/or cystoscopy
3. Complete blood count (CBC), renal and liver function tests
4. Alkaline phosphatase
5. Bone scan
6. Chest x-ray (CXR)

Management/Treatment

1. Preparation for therapy: CBC, creatinine
2. Complete resection or adequate tissue sampling
3. Radical cystectomy with full bilateral pelvic lymph node dissection
4. Transurethral resection of bladder tumour (TURBT) ± radiotherapy or chemotherapy
5. Bladder-preserving approach consisting of radiotherapy combined with platinum-based chemotherapy
6. Neoadjuvant/adjuvant chemotherapy (cisplatinum or carboplatinum-based, gemcitabine, paclitaxel)
7. Second-line chemotherapy (cisplatin, methotrexate, vinblastine [CMV] or methotrexate, vinblastine, adriamycin, and cisplatinum [MVAC])
8. Single modality therapy (chemotherapy or radiotherapy) for palliation or survival

9. Follow-up (urine cytology, CT abdomen and pelvis, CXR, cystoscopy ± biopsy and cytology)

Major Outcomes Considered

- 5-year, disease-free, disease-specific, recurrence-free, median, and overall survival rates
- Presence of residual disease
- Bladder preservation rates
- Rates of superficial, muscle-invasive, or distant recurrences
- Overall recurrence rate
- Rates of metastasis

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- What work-up is required for bladder cancer?
- What is the appropriate stage-specific treatment (i.e., surgery, systemic therapy, radiotherapy) for patients with bladder cancer?
- Following treatment for bladder cancer, how often should patients be followed and what tests are appropriate during the follow-up period?

Search Strategy and Revision History

The original guideline, which was developed in 2005 and updated in 2009, 2010, and 2011, was divided into 2 distinct documents during the 2013 update: a guideline on noninvasive bladder cancer (GU-009) and a guideline on muscle-invasive and locally advanced or unresectable/metastatic disease (GU-002). The guideline on invasive disease includes an update of the literature, using the Medline and EMBASE databases. The search term *bladder cancer* was used and results were limited to clinical trials, randomized controlled trials, and phase III studies.

The guideline was again updated in 2013. The literature review was updated with new clinical trials published between 2010 December and 2013 March. For this update, the PubMed database was searched using the terms ("transitional cell carcinoma" or "urothelial carcinoma") AND "bladder." Results were limited to clinical trials published in English, leaving a total of 80 citations. Phase I clinical trials, as well as irrelevant citations (i.e., studies on primaries other than bladder cancer, studies on lifestyle interventions, etc.) were subsequently removed, leaving a total of 5 phase III clinical trials, 2 additional randomized controlled trials, and 8 phase II trials, all of which were included in the review.

Number of Source Documents

- The 2011 literature update produced a total of 15 relevant citations, which were included in the review.
- The 2013 update produced a total of 5 phase III clinical trials, 2 additional randomized controlled trials, and 8 phase II trials, all of which were included in the review.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment and management of muscle invasive and locally advanced/metastatic bladder cancer

Potential Harms

Chemotherapy toxicity, including leukopenia, febrile neutropenia, thrombocytopenia, and bleeding

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Genitourinary Tumour Team. Muscle invasive and locally advanced/metastatic bladder cancer. Edmonton (Alberta): CancerControl Alberta; 2013 Oct. 17 p. (Clinical practice guideline; no. GU-002). [85 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Jan (revised 2013 Oct)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Genitourinary Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, nurses, pathologists, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Genitourinary Tumour Team. Bladder cancer. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Jan. 16 p. (Clinical practice guideline; no. GU-002).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 24, 2012. The information was verified by the guideline developer on February 13, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on May 22, 2014. This summary was updated by ECRI Institute on February 15, 2017 following the U.S. Food and Drug Administration advisory on general anesthetic and sedation drugs.

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